RLL-45000

IB/03/05331

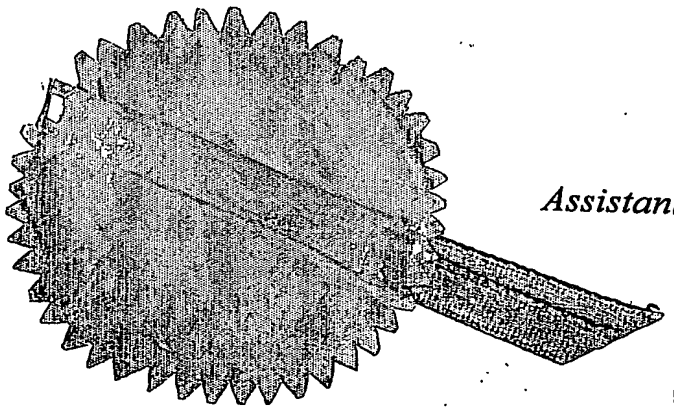
सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Provisional Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.**1239/Del/02** dated **11th December 2002.***

Witness my hand this 23rd day of February 2004.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

1239/02

1 1 DEC 2002

D305/12

FORM 1

Govt. of India Patent Office
New Delhi
Received Rs. 5000/- in cash.
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on 11 DEC 2002
Vide Entry No. 314 in the
Register of Valuables
A. O ..... Cashier

THE PATENTS ACT, 1970
(39 of 1970.)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **" PROCESS FOR THE PREPARATION OF NOVEL MONO N-METHYL PYRROLIDONE MONOHYDRATE SOLVATE OF LORACARBEF "**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. NEERA TEWARI

c. HASHIM NIZAR POOVANATHIL NAGOOR MEERAN

d. BISHWA PRAKASH RAI

e. SHAILENDRA KUMAR SINGH

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 6343126; 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, YATENDRA KUMAR, NEERA TEWARI, HASHIM NIZAR POOVANATHIL NAGOOR MEERAN, BISHWA PRAKASH RAI, SHAILENDRA KUMAR SINGH of Ranbaxy Laboratories Limited, Plot No. 20, Sector - 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, Ranbaxy Laboratories Limited, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a. (YATENDRA KUMAR)

b. (NEERA TEWARI)

c. (HASHIM NIZAR POOVANATHIL NAGOOR MEERAN)

d. (BISHWA PRAKASH RAI)

e. (SHAILENDRA KUMAR SINGH)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:
   a. Provisional Specification (3 copies)
   b. Drawings (3 copies)
   c. Statement and Undertaking on FORM – 3
   d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 000064 dated 30.11.2002 on ANZ Grindlays Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this 9TH day of DECEMBER, 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2 1239

The Patents Act, 1970 11 DEC 2002
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

PROCESS FOR THE PREPARATION OF NOVEL MONO N-METHYL PYRROLIDONE MONOHYDRATE SOLVATE OF LORACARBEF

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019
(A Company incorporated under the Companies Act, 1956)

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of mono-N-methyl pyrrolidone monohydrate solvate of loracarbef, a convenient intermediate for preparing loracarbef.

Loracarbef is a synthetic β-lactam antibiotic of the carbacephem class for oral administration. Loracarbef is disclosed by Hashimoto et al., in U.S. Patent No. 4,335,211.

Hashimoto et al has disclosed a class of 1-carbacephalosporins having desirable antibiotic and oral activity characteristics. These compounds have been evaluated for the treatment of various conditions such as common upper and lower respiratory tract infections caused by the pathogen H. influenza. One such compound, 7-(R)-phenylglycinamido-3-chloro-1-azabicyclo[4.2.0]oct-2-ene-8-one-2-carboxylic acid, known as Loracarbef, has shown activity against a broad spectrum of bacteria in laboratory tests. Loracarbef has proven to be a relatively stable compound, which exhibits high blood levels and relatively long half-life.

Loracarbef is chemically (6R,7S)-7-[(R)-2-amino-2-phenylacetamido]-3-chloro-8-oxo-1-azabicyclo [4.2.0]oct-2-ene-carboxylic acid, monohydrate having structural formula I as shown in the accompanied drawings.

Loracarbef has been isolated in various forms, including the crystalline monohydrate form (which is the drug) disclosed in the European patent publication EP 0311,366. Other solvate forms of the compounds known are bis (DMF), dihydrate mono(DMF) and mono (DMF) forms and are disclosed in US Patent No. 4,977,257. The crystalline dihydrate form of loracarbef is disclosed in European patent publication, EP 0369,686; crystalline anhydrate form of loracarbef disclosed in US Patent No. 5,580,977, which is converted to crystalline monohydrate having specific bulk density.

The solvates referred above are convenient intermediate for preparing loracarbef in general and to the monohydrate form of loracarbef specifically. Accordingly, methods for the total synthesis of these promising compounds and intermediates to these compounds are highly desirable, particularly methods, which are adaptable to large scale manufacture, and result in high yields and reduced cost of manufacture.

It is a well known fact that in order to formulate a bulk product it is critical that the compound intended for pharmaceutical use to have sufficient density such that the product could be

formulated for pharmaceutical use. For loracarbef monohydrate, a density of greater than or equal to 0.5 g/ml is desired in order to facilitate the formulation of the bulk product.

As per the process described in EP 0,369,686, the crystalline monohydrate form of loracarbef may be prepared by first suspending loracarbef dihydrate in water and then effecting solution by the addition of acid followed by the adjustment of the pH with base, or by the addition of base followed by acid. The resultant loracarbef may be crystallized and then isolated by filtration.

However, this process is considered commercially unattractive because it yields loracarbef monohydrate in the form of a fine, fluffy powder with a density of approximately 0.2 g/ml. This density renders the bulk product, loracarbef monohydrate, very difficult to formulate. Since this compound is intended for pharmaceutical use, the ability to formulate the bulk product is critical. For loracarbef monohydrate, a density of greater than or equal to 0.5 g/ml is desired in order to facilitate the formulation of the bulk product. Thus, it was necessary to improve the process of EP 0,369,686, in order to obtain a bulk product with a sufficient density such that the product could be formulated for pharmaceutical use.

What is needed in light of the above difficulties is a process for preparing crystalline loracarbef monohydrate with specific bulk density in a more efficient manner.

The present invention provides an efficient process for preparing loracarbef monohydrate having the desired bulk density.

The first aspect of the present invention is directed to the process of preparing mono N-methyl pyrrolidone monohydrate solvate of loracarbef having the X-ray powder diffraction pattern listed in the Table as specified in the Example.

Another aspect of the present invention is directed towards the facile conversion of mono N-methyl pyrrolidone monohydrate solvate of loracarbef to loracarbef monohydrate that results in a commercially desirable form of the bulk product.

Yet another aspect of the present invention is directed towards a process for preparing crystalline loracarbef monohydrate having a bulk density greater than or equal to 0.6 gm/ml.

Accordingly, the present invention provides a process for the preparation of mono- N-methyl pyrrolidone monohydrate solvate of loracarbef of structural formula II as shown in the accompanied drawings. The process comprises mixing the compound of formula III wherein R_1 is hydrogen, trihalo (C_1-C_4 alkyl), C_1-C_4 alkyl, C_1-C_4 substituted alkyl, C_1-C_4 alkoxy, C_1-C_4 substituted alkoxy, C_1-C_6 alkylthio, C_1-C_6 substituted alkylthio, methoxy methyl, carbamoyloxy methyl, acetoxymethyl, C_2-C_6 alkenyl, C_2-C_6 substituted alkenyl, or halogen such as bromo, chloro, fluoro, and iodo; R_2 is a carboxy-protecting group with N-methyl pyrrolidone and a cyclic amine base containing 0-1 oxygen atoms or dimethyl benzylamine, to form the free amine of the compound of formula IV and thereafter, without isolating the free amine, mixing the free amine with an acylating agent of the formula V wherein R_3 is an amino protecting group and L is a leaving group.

The term "carboxy-protecting group" refers to one of the ester derivatives of a carboxylic acid group which is not sterically hindered and are commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such groups are allyl, alkyl, benzyl and substituted benzyl groups, silyl group and halo-substituted alkyl groups such as the 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, and 2-iodoethyl groups. Further examples of these groups are found in E. Haslam, "Protective Groups in organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 5. A preferred ester group is the 4-nitrobenzyl group.

The term "amino-protecting group" refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound.

The amino protecting group R_3 of Formula V is selected from either the carbamates such as t-butoxycarbonyl or benzyloxycarbonyl, or the enamines. Preferred amino-protecting groups are the t-butoxycarbonyl, phenoxyacetyl, and enamines derived from (C_1-C_4 alkyl)acetoacetate groups. Similar amino-protecting groups used in the cephalosporin, penicillin and peptide art are also embraced by the above terms. Further examples of groups referred to by the above terms are described by J. W. Barton, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 2, and T. W. Greene, "Protective Groups in organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 7.

The term "leaving group" means a leaving group which, under the reaction conditions will leave, allowing the free amine to bond to the carbonyl group. Leaving groups include those where L is of the formula VI where R_4 is C_1-C_6 alkyl, or L is Cl, Br, I, active esters such as p-nitrophenyl; the adducts of dicyclohexylcarbodiimide.

The base used is selected from the group consisting of 5 or 6 membered tertiary cyclic amines which may contain an oxygen atom, or dimethyl benzylamine. Preferable tertiary cyclic amine bases are N-methyl morpholine (NMM) and N-methyl piperidine (NMP). The base is preferably in an amount of between about 1 to 1.3 molar equivalents, and most preferably at about 1.13 molar equivalents. Preferably N-methyl morpholine (NMM) is used.

The hydrochloride salt of formula III is prepared by the process described in the European Patent Application 0266896.

In forming the free amine (IV) a sufficient amount of base is added to the hydrochloride salt to neutralize the compound and form the free amine. In the preferred method for producing the free amine, the hydrochloride salt (III) is neutralized by adding it to a stirred mixture of N-methyl pyrrolidone of such a volume that the final solution will be about 0.5M, and between about 1 to 1.3 equivalents of N-methyl morpholine (NMM), at ambient temperature. The mixing initially occurs at room temperature (20°C) for a time between about 10-20 minutes, and then it is cooled to a temperature of between about -5 to -10°C.

The mixed anhydride of formula V is prepared by adding about 1.2 equivalents of the Dane salt (Et, K)-2(R)-2-phenyl-(2)-ethylbert-2-ene-3-yl)amino)acetate of Formula VII (which may be prepared according to the procedure of Dane et al., Angew. Chem., Vol. 74, 873 (1962), with a volume of N-methyl pyrrolidone sufficient to result in a concentration of about 0.25M, and stirring the mixture at ambient temperature for 20-60 minutes. The mixture is then cooled to -20 to -15°C and N- methyl morpholine (NMM) (0.025 equivalents) and methanesulfonic acid (0.05 equivalent) are added. Ethyl chloroformate (1.17 equivalent) is then added and the mixture stirred for 1 to 2 hours, thus resulting in the mixed anhydride (V).

The amino- and carboxy- protecting groups are removed by methods well known in the art. Examples of conditions for the removal of these two types of protecting groups can be found in standard works on the subject, such as E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapters 2 and 5, and T. W. Greene,

"Protective Groups in Organic Synthesis", John Wiley and Sons, New York, N.Y., 1981, Chapters 5 and 7, respectively.

The acylation method in the present invention comprises adding the cooled free amine mixture (IV) to the mixed anhydride (VIII) over a period of 10-20 minutes, while keeping the internal reaction temperature between –20° and -10°. The reaction is stirred for 60 minutes.

For deprotecting the protected amino and protected carboxy group, a mixture of concentrated HCl in water (2:1) at a temperature of 0° to -10°C, is added drop wise to the acylation solution (III). Zinc dust (3.5 equivalents) is then added keeping the temperature from about 0° to +5°C. Temperature was raised to 20-25°C. The mixture is stirred for 60 minutes at 20-25°C and semi-carbazide hydrochloride (1.15 equivalents) is added, followed by 30-60 minutes of stirring. The pH is adjusted to 2.9-3.0 with 28% aqueous ammonia and the mixture is filtered and washed with N-methyl pyrrolidone. The pH is adjusted to a 4.8 to 5.0 using 28% aqueous ammonia. Solid separates from the solution and the reaction mixture is stirred for 30 minutes, and the pH is continuously adjusted to 5.8-6.2. The temperature of the mixture is lowered to 20-25°C and added a polar solvent such as acetonitrile to it and stirred for another 30 minutes before being filtered. The crystals are collected by filtration, and dried to give N-methyl pyrrolidone monohydrate solvate of loracarbef.

The process disclosed results in high yields of compounds of formula II yields, (> 90%).

It will be understood that the listing for substituents is exemplary and not exhaustive, and equivalents are expected to be encompassed by the spirit of the invention.

As mentioned above, mono N-methyl pyrrolidone monohydrate solvate of loracarbef is useful as an intermediate to loracarbef monohydrate. Surprisingly, the loracarbef monohydrate prepared from the mono N-methyl pyrrolidone monohydrate solvate of loracarbef is found to have a bulk density equal to or greater then 0.6 g/ml.

The monohydrate is prepared suspending mono N-methyl pyrrolidone monohydrate solvate of loracarbef in water. The most common procedure is to effect solution of the starting material by the addition of a minimum amount of acid, generally 6N (or more dilute) hydrochloric acid. Temperature of the solution was raised to about 50° C and slowly added 28% ammonia solution to the solution until a pH of approximately 4.5-4.8 is obtained. The gradually

developing suspension is stirred and maintained at about 50° C, during the addition of the base. The warm pH-adjusted suspension (50°C) is cooled to approximately 20°C, stirred, filtered (such as on Buchner funnel) and the collected solid dried at 40-45°C to yield crystalline loracarbef monohydrate having bulk density equal to or greater than 0.6 g/ml.

In the following section preferred embodiments are described by a way of example to illustrate the process of the invention. However, these are not intended in any way to limit the scope of the claims.

In the following Example, the terms nuclear magnetic resonance spectra, mass spectrum and infrared spectroscopy are abbreviated NMR, MS and IR, respectively.

In conjunction with the NMR spectra, the following abbreviations are used: "s" is singlet, "d" is doublet, "t" is triplet, "q" is quartet, and "m" is multiplet.

The NMR spectra were obtained on a Bruker (DRX 300) 300 MHz instrument. The chemical shifts are expressed in ppm values (parts per million downfield from tetramethylsilane).

EXAMPLE 1

Step A :

Preparation of N-methyl morpholine salt

To a mixture of N-methyl pyrrolidine (60 ml) and N-methyl morpholine (3.0 g), added p-nitrobenzyl 7 β-amino-3-chloro-1-carba (1-dethia)-3-cephem-4-carboxylic acid hydrochloride (10.0 g) over 15-20 minutes at –20 to -15°C. The reaction mixture was stirred for 60 minutes.

Step B :

Preparation of mixed anhydride

The Na/K Dane salt (VII) (9.5 g) was suspended in N-methyl pyrrolidone (120ml) and stirred for 30-35 minutes. The reaction mixture was cooled to –20 to – 15°C and added methane sulphonic acid (0.15 g) and N-methyl morpholine (0.08 g) to it. Ethyl chloroformate (3.3 g) was further added in one portion and stirring was continued for 60-90 minutes at –10 to -15°C.

Step C :

Condensation :

N-methyl morpholine hydrochloride solution containing the free amine obtained from Step A was slowly added to the mixed anhydride obtained from Step B at -20° to -10°C in 15-20 minutes. The reaction mixture was stirred for 60 minutes. Conc. HCl in H_2O (28 ml in 14 ml H_2O) was added drop wise at -10° to 0°C to diprotected loracarbef followed by adding zinc powder (6.0g), while maintaining the temperature from 0° to +5°C. The temperature was raised to 20-25°C and stirred the reaction mixture for about 60 minutes. Semicarbazide hydrochloride (3.3 g) was added and the stirring was continued for 30 minutes. The pH of the reaction mixture was adjusted to 2.9 to 3.0 with 28% NH_3 solution and then filtered it. The filtrate was washed with N-methyl pyrrolidone (50 ml) and adjusted the pH at 4.8 to 5.0, solid was separated from the solution, stirred the mixture for 30 minutes and finally adjusted the pH at 5.8 to 6.2. The reaction mixture was cooled to 20-25°C, added acetonitrile (60ml) and stirred for another 30 minutes. It was then filtered and the solid was dried under vacuum to give mono N-methyl pyrrolidone monohydrate solvate of loracarbef which was characterized on the basis of the data given below.

NMR (300 MHz) (δ): 7.4 (s, 5H, ArH), 5.3 (d, 1H, β-lactam), 5.2 (s, 1H, CH, Ph), 3.83 (m, 1H, β-lactam), 3.3-3.42 (t, 2H, due to N-methyl pyrrolidone), 2.72 (s, 3H, N-CH_3, due to NMP), 2.46-2.53 (m, 2H, CH_2), 2.32-2.37 (t, 2H, due to NMP), 1.90-1.95 (m, 2H, due to NMP), 1.55(m, 1H, CH), 1.18-1.22 (m, 1H, CH)

Moisture content (by KF): 5.0% w/w

IR (KBr disc): 2980 – 3650 (s, and broad) 1780, 1720, 1690, 1600, 1580, 1460, 1400,

X-Ray Powder Diffraction obtained on a Rigaku (RINT 2000) instrument with nickel-filtered copper radiation (Cu:Ni) of wavelength lambda 1.5406 Angstrom. The interplanar spacings are in the column marked "d" and are in Angstroms and the relative intensities are in the column marked "I/I_1 ".

D	I/Io
15.8248	14
15.2251	13
12.0338	100
8.0954	8
7.5189	33
5.9968	13
5.4668	12
5.3810	14
5.2605	18
4.8863	22
4.7513	37
4.4579	21
4.2997	22
4.1411	16
3.9939	55
3.6421	38
3.3858	18
2.7314	15

EXAMPLE 2

Preparation of loracarbef monohydrate from mono N-methyl pyrrolidone monohydrate solvate

Loracarbef mono N-methyl pyrrolidone monohydrate solvate (10.0 g) was suspended in water (80 ml). 12N hydrochloric acid (1.0 ml) was added to obtain a clear solution. Added activated carbon (1.0 g) and stirred the reaction mixture for 30-40 minutes. The suspension was then filtered and washed with water (30 ml). Temperature of the filtrate was raised to 50-55°C and slowly adjusted the pH at 1.8 – 1.9 with 8% NH_3 solution. The reaction mixture was stirred for 30 minutes at 50-55°C and adjusted the pH to 4.5 to 4.8 slowly in 30-35 minutes with stirring at 50-55°C. Stirring continued for additional 30 minutes and then slowly cooled to 20-25°C. The

slurry was washed with water. The cake was dried in air oven at 40-45°C to yield crystalline loracarbef monohydrate (5.0 g) having bulk density greater than 0.6 g/ml.

IR, NMR and X-Ray diffraction pattern of the crystalline loracarbef monohydrate maiches with the authentic samples of crystalline loracarbef monohydrate.

Dated this 10TH day of December, 2002.

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

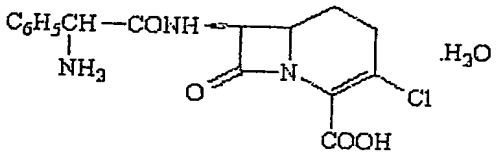
Application No.

No. of sheets = 09

Sheet 01 of 09

1239

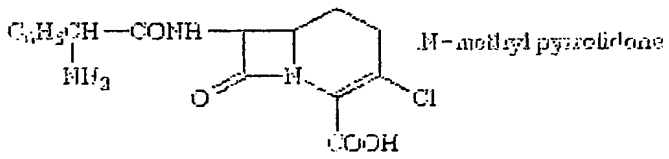
11 DEC 2002



FORMULA - I

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



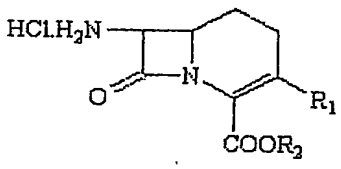
FORMULA - II

For Ranbaxy Laboratories Limited

(Onkar Nath Tikoo)
Company Secretary

1239-02

11 DEC 2012



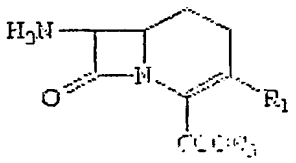
FORMULA - III

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1839/DEL/2007

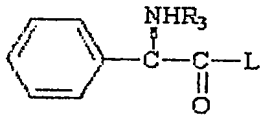
11 DEC 2007



FORMULA - IV

For Ranbaxy Laboratories Limited

(Sushil Kumar Paliwari)
Company Secretary

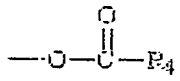


FORMULA V

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1 1 DEC 2002



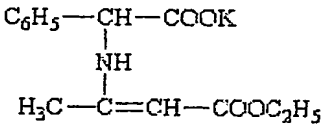
FORMULA VI

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1239-DEL-2002

11 DEC 2002

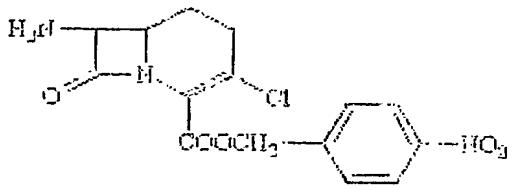


FORMULA VII

ORIGINAL

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



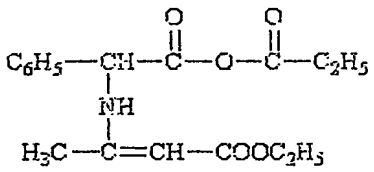
FORMULA - VIII

For Ranbaxy Laboratories Limited

(Sushil Kumar Kalawati)
Company Secretary

1239-DEL-2012

11 DEC 2012



FORMULA IX

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

PCT Application

IB0305331